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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/575,554	05/22/2000	Brett P. Monia	ISPH-0463	1277

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 03/05/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.	Applicant(s)
09/575,554	Monia et al
Examiner	**Art Unit**
Jeffrey Fredman	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Feb 11, 2002* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☒ The period for reply expires *three* months from the mailing date of the final rejection.

b) ☐ In view of the early submission of the proposed reply (within two months as set forth in MPEP § 706.07 (f)), the period for reply expires on the mailing date of this Advisory Action, OR continues to run from the mailing date of the final rejection, whichever is later. In no event, however, will the statutory period for the reply expire later than SIX MONTHS from the mailing date of the final rejection.

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will be entered upon the timely submission of a Notice of Appeal and Appeal Brief with requisite fees.

3. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search. (See NOTE below);

   (b) ☐ they raise the issue of new matter. (See NOTE below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

4. ☒ Applicant's reply has overcome the following rejection(s):
   The double patenting rejections are withdrawn.

5. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claim(s).

6. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
   See attached sheet.

7. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

8. ☒ For purposes of Appeal, the status of the claim(s) is as follows (see attached written explanation, if any):
   Claim(s) allowed: *None*
   Claim(s) objected to: *None*
   Claim(s) rejected: *1 and 7-20*

9. ☐ The proposed drawing correction filed on _____ a) ☐ has b) ☐ has not been approved by the Examiner.

10. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.

11. ☐ Other:

JEFFREY FREDMAN
PRIMARY EXAMINER
ART UNIT 1637

Response to Arguments

1. Applicant's arguments filed February 11, 2002 have been fully considered but they are not persuasive.

Applicant's filing of the terminal disclaimer overcomes the double patenting rejection. Also, the cancellation of claim 6 eliminates the statutory double patenting rejection.

However, the prior art rejection remains applicable. Applicant argues that the rejection does not establish a prima facie case of obviousness. The references teach and suggest every element, and provide motivation to make the compounds. As noted with relation to this subject matter, it is the combination of references that provides the rejection. Bos provides the requisite sequence information for Ki-ras. Motivation is provided by several of these references. Saison-Behmoaras states "It has been found that 10-20% of human tumors have a mutation in one of the three ras genes (Ha-ras, Ki-ras, N-ras) leading to the production of p21 ras oncoproteins, which are thought to play an important role in the transformed phenotype (page 1111, column 1)". Here, Saison-Behmoaras discloses the equivalence of the three ras oncogenes and provides a strong and direct motivation to inactivate each of these genes, since they are found activated in 10-20% of human tumors. Saison-Behmoaras continues "In order to study the biological effects of ras expression in the context of molecular biology of ras-dependent pathway and to provide a rational basis for the development of antitumor drugs we are investigating the use of antisense oligonucleotides and their modified analogues, which upon hybridization to complementary mRNA sequences, interfere with translation and thus can be employed for sequence-specific control of gene expression. In an attempt to inhibit the expression of an oncogene, application of antisense oligonucleotides has proved to be a

powerful tool (page 1111, column 1 to column 2)". This quote demonstrates that Saison-Behmoaras provides a motivation to utilize antisense oligonucleotides to achieve the goal, as noted above, of inactivation of ras oncogenes, since antisense oligonucleotides were known to be a powerful tool to interfere with translation and gene expression of the ras oncogenes and since the antisense oligonucleotides could provide a rational basis for drug development. Further motivation is provided by Daaka, who states "The ras family of mammalian protooncogenes includes three members, termed Ha-ras, Ki-ras, and N-ras, that are likely to play a fundamental role in basic cellular functions based on their high degree of conservation throughout eukaryotic evolution (ref omitted). The amino acid sequence of the ras gene products all contain GTP-binding consensus regions and are thought to be localized to the inner surface of the plasma membrane (ref omitted). In mammals, ras proteins have been implicated in cellular proliferation (ref omitted) and terminal differentiation (ref omitted). Point mutations in ras oncogenes that alter the enzymatic properties and/or cause overexpression of the ras p21 oncoprotein may be causatively or closely linked ot the onset of some types of human tumors (refs omitted) (page 267, columns 1 and 2)." Daaka here also motivates the ordinary practitioner to inactivate mutated ras proteins, including any of the three equivalents, Ha-ras, Ki-ras or N-ras. Daaka also teaches the use of antisense methodologies to perform this inactivation (page 267, column 2 to page 268, column 1). Bos et al also motivates the inactivation of the ras oncogene, though Bos does not suggest an antisense mechanism " The human gene family consists of three members: the H-ras, K-ras and the N-ras gene (1) These genes code for related proteins of 21kD, which are located at the inner face of the cell membrane (36) and are thought to be involved in transducing signals from cell surface receptors to their intracellular targets (37). A significant portion of tumor cell

lines and fresh tumor tissue has been found to possess an activated ras gene. Such genes are characterized by their ability to induce oncogenic transformation of mouse 3T3 cells. In most cases so far analyzed the activation is due to a point mutation in the 12th or 61st codon of a ras gene resulting in a single amino acid substitution in the gene product (column 1, lines 14-26)". These three references each note the linkage and potential causative nature of ras oncogenes with human tumors. Each reference discloses that three different, but functionally and structurally equivalent ras oncogenes termed Ha-ras, Ki-ras and N-ras are involved in human tumors. Saison-Behmoaras and Daaka explicitly motivate the inactivation of these proteins by antisense mechanisms to inhibit tumor formation and growth. These references thus provide explicit motivation for the ordinary practitioner to inactivate Ki-ras in order to inhibit tumor formation and growth.

The references direct the practitioner to codon 12 and 61 mutations and the 5' or 3' UTR of Ki-ras. Saison-Behmoaras states "In the ras gene family, activation of the protooncogene to form the oncogene is due to point mutations, most often in the 12th and 61st codons (page 1111, column 2)". This statement is generic to all three ras gene family members, including Ki-ras. This statement also directs the ordinary practitioner to design antisense oligonucleotides at these two sites, which is completely constrained by the known sequence of Ki-ras. Given the teachings noted above for the equivalence of the three ras genes, an ordinary practitioner would have designed probes for each gene equivalent to known working probes. Daaka discloses, on page 272, column 1, working 5' UTR probes for Ha-ras, which would direct the practitioner to design equivalent probes for Ki-ras. Ki-ras is known to be so identical to Ha-ras that they function identically and identical common mutations at codons 12 and 61 are responsible for aberrant function. Further motivation

would be provided by Uhlmann, who states under the subheadings "Selection of effective target sequences" on page 576 that "As is evident from figure 47, a large number of target sequences are suitable for inhibiting gene expression. At the level of translation, these are the 5' non coding regions, the ribosome binding site, the translation start region, the coding region, and the 3' non translated region (page 576, column 1 paragraph 1)". Uhlmann explicitly directs the ordinary practitioner to the 5' UTR and the 3'UTR for selection of effective target sequences.

The last element of a prima facie case of obviousness is the requirement for a reasonable expectation of success. With regard to Applicant's argument on expectation of success, the MPEP 2143.02 states "The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success." Two references which relate to Ha-ras support the rejection on this point. Daaka, a reference in which antisense oligonucleotides were synthesized based on secondary structure considerations and tested against a closely related protein, Ha-ras, demonstrates that all three tested oligonucleotides exhibited antisense inhibitory function. This evidence supports a reasonable expectation of success, since 100% of the tested oligonucleotides met the test requirements. Saison-Behmoaras also demonstrates that antisense oligonucleotides have a reasonable expectation of success. Saison-Behmoaras shows 7 different H-ras specific antisense oligonucleotides (see page 1112, figure 1) of which 6 demonstrate acceptable antisense activity. This 85% success rate also supports the reasonable expectation of success. Applicant has provided no evidence for the allegation that synthesis of antisense oligonucleotides would lack a reasonable expectation of success. Further, Daaka, on page 267, column 1 to page 267, column 2, details eleven papers discussing successful uses of antisense oligonucleotides including three targeted against Ha-Ras.